FDA Briefing Document

Oncologic Drugs Advisory Committee
March 21, 2012

NDA: 202497
Vincristine Sulfate Liposomal Injection (Marqibo)
Talon Therapeutics

DISCLAIMER STATEMENT

The attached documents contain background material prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are presenting the Marqibo NDA with the applicant's proposed indication "for the treatment of adult patients with Philadelphia Chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy" to this Advisory Committee in order to gain the Committee's insights and opinions. This background package may not contain all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all internal reviews have been finalized. The final determination may be affected by issues not discussed at this meeting.

This document is based on the applicant's original NDA submission and subsequent information as provided up to February 14, 2012.

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List of Abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ANC	Absolute Neutrophil Count
BM	Bone Marrow
BMBx	Bone Marrow Aspiration and Biopsy
BSA	Body Surface Area
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Remission
CRi	Complete Remission with incomplete blood count recovery
CRp	Complete Remission with incomplete platelet recovery
CRF	Case Report Form
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HI	Hematologic Improvement
HSCT	Hematopoietic Stem Cell Transplantation
IRRC	Independent Response Review Committee
ITT	Intent-to-Treat
IV	Intravenous
IWG	International Working Group
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's Lymphoma
ODAC	Oncologic Drugs Advisory Committee
OS	Overall Survival
Ph-	Philadelphia Chromosome Negative
PR	Partial Remission
PS	Performance Status
SAE	Serious Adverse Event
SD	Stable Disease
Std	Standard Deviation
TEAE	Treatment Emergent Adverse Event
VCR	Vincristine
VSLI	Vincristine Sulfate Liposomal Injection (Marqibo)

1. Applicant's Proposed Indication, Dose and Schedule

Marqibo (Vincristine Sulfate Liposomal Injection, VSLI) is indicated for the treatment of adult (age ≥18 years) patients with Philadelphia Chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy. Marqibo is administered at a dose of 2.25 mg/m^2 IV every 7 days as a 60 minute infusion for a 28-day course of treatment.

2. Executive Summary

Marqibo is a liposomal formulation of vincristine, which has been developed with the intention to increase the tolerable dose of the active moiety, vincristine, while reducing its dose limiting neurotoxicity. Marqibo's NDA 202497 is a 505 (b) (2) submission based on the results of a phase 2 single arm study, HBS407, supported by a phase 1/2 single arm dose finding study, VSLI-06. Study HBS407 was an international, multicenter, open-label, single-arm trial to evaluate the effect of VSLI in adult patients with Ph- ALL in second or greater relapse, or Ph- ALL who failed two or greater number of treatment lines of anti-leukemia chemotherapy. The primary efficacy endpoint of Study HBS407 was the proportion of the patients who achieved CR+CRi.

Efficacy: Per FDA review, the rate of CR+CRi in the study HBS407 was 15.4% (10 out of 65) with 3 CRs and 7 CRis. Due to the lack of subsequent bone marrow evaluations, two of the Applicant's reported responses were not confirmed; thus the durability of these responses is unknown. The median duration of CR+CRi for the 8 remaining patients, defined as the first date of CR+CRi to the date of the last available assessment of the same response, was 28 days. Of patients who did not achieve CR+CRi after Marqibo, 7 patients underwent HSCT. Six of the 7 patients received multi-agent chemotherapy regimens prior to subsequent HSCT. The Applicant reported other endpoints including overall survival. Overall survival analysis in a single arm study is exploratory and difficult to interpret because the result may be heavily influenced by other non-drug factors.

Safety: The long-standing clinical experience with standard vincristine has demonstrated a safety profile most notable for peripheral sensory and motor neuropathy as well as autonomic polyneuropathy and myelosuppression. The evaluation and interpretation of neuropathy in a single arm study involving patients who received prior multi-agent chemotherapies including vincristine is complicated. Neuropathy-associated adverse events during the VSLI treatment period were reported in 72 out of 83 (86.7%) patients who received 2.25 mg/m^2 of Marqibo, and neuropathy AEs of Grade ≥3 in 27 (32.5% of the 83 treated with 2.25 mg/m^2). Eleven (13.3% of the 83 treated with 2.25 mg/m^2) patients reported serious AEs related to neuropathy. In study HBS407, 15 (23.1%) patients died during the treatment period (i.e. from the first dose infusion date through last dose date plus 30 days). Overall, 96.4% of patients who received 2.25 mg/m^2 of Marqibo reported AEs of Grade ≥3 and 75.9% of patients reported any serious AE.

Issues with the submission:
1. Available Therapy
2. Benefit/Risk

Given the magnitude of CR and CRi rates and the safety profile observed, we ask the Oncologic Drugs Advisory Committee to discuss the risks and benefits of Marqibo for the treatment of adult (age ≥18 years) patients with Philadelphia Chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.

3. Background

3.1. Frontline and salvage treatment options for adult patients with Philadelphia Chromosome negative ALL

In the United States, of 5300 new cases of ALL reported annually, approximately 2000 are in adults (age ≥18 years). Seventy percent (1400 subjects) of new annual cases of adult ALL are Ph-.[1] Based on published treatment response rates and treatment-related mortality rates, approximately 500 patients per year are in second or greater relapse and require second or greater salvage therapy.[2, 3, 4]

Significant success in the treatment of ALL in pediatric patients has been built on combinations of multiple anti-leukemic drugs that are delivered in a sequence of extended courses. A similar strategy has been proposed for the first line treatment of ALL in adult patients.[5] Vincristine, corticosteroids, anthracyclines and asparaginase continue to be the effective chemotherapy backbone for treatment of ALL. Cyclophosphamide, cytarabine (ara-C), etoposide, teniposide, methotrexate, and 6-mercaptopurine are other chemotherapeutic agents that have been used in treatment of ALL. Postremission therapy is comprised of intensified consolidation and maintenance therapy or HSCT.

Approximately 60-70% of patients relapse after the first-line of therapy or are refractory to it. Remission rates ranging 20-80% have been reported in adults with refractory ALL or after the first relapse of ALL.[3, 6] Remissions after the first salvage therapy, if achieved, are usually short with median durations ranging from 2 to 7 months.[3, 6] Adults with relapsed Ph- ALL have 5-year survival of approximately 7%. [2, 7] First salvage therapy for Ph- ALL in adults may consist of a patient's original front-line induction regimen with different dose intensities with or without additional chemotherapeutic agents. There have been many proposed first salvage therapy regimens, but none has emerged as definitive and standard therapy.

The majority (~70%) of patients who achieve a CR due to the first salvage therapy subsequently relapse and become candidates for second salvage therapy. Heterogeneous salvage regimens were reported in a retrospective assessment of the outcomes of 288 adults with ALL after second salvage therapy.[4]

3.2. Regulatory background related to Marqibo

Drug development program for Marqibo began in 1999 with the original Investigational New Drug (IND) submission. In September 2003, Inex Pharmaceuticals submitted a New Drug Application (NDA) for accelerated approval of Marqibo for "the treatment of patients with aggressive non-Hodgkin's Lymphoma (NHL) that is refractory to or relapsed after two prior combination chemotherapy regimens". This NDA was based primarily on results from an international, multicenter, single arm study in patients with relapsed, aggressive NHL. The study enrolled 119 patients with relapsed NHL. Based on central pathology review and FDA analysis of incomplete baseline staging for NHL, only 72 patients were eligible for evaluation. The response rate was 21% (95% CI: 12-32), with a complete response (CR) rate of 1%. The duration of response could not be adequately determined because two thirds of the patients dropped out prior to tumor progression. The median duration of response in the 11 confirmed responders who were histologically eligible and had no major protocol violations was 85 days.

ODAC discussed the results of this trial on December 1, 2004. The committee unanimously agreed that these results were not predictive of clinical benefit and should not be the basis of approval under Subpart H. For a drug to be approved under subpart H, the drug must demonstrate an improvement over available therapy. Per ODAC discussion and committee voting, Marqibo did not demonstrate an improvement over available therapy. The committee recommended a randomized clinical trial to demonstrate the clinical benefit of Marqibo for the treatment of patients with aggressive non-Hodgkin's Lymphoma.

Talon Pharmaceuticals (formerly Hana Biosciences) obtained the rights to develop Marqibo from Inex in 2006. In July 2011, Talon submitted the Current NDA 202497 seeking accelerated approval (subpart H) for Marqibo for the treatment of adult (age $\geq$18 years) patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy based on a Phase 2 Study HBS407 and supporting Phase 1/2 Study VSLI-06.

Throughout Marqibo's drug development program, FDA recommended randomized clinical trials to demonstrate the potential clinical benefit of Marqibo.

There is no FDA approved drug for the current proposed indication for the treatment of adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.

3.3. Accelerated Approval

Applicants submitting New Drug Applications (NDAs) and Biologics License Applications (BLAs) to the FDA are required to demonstrate the products to be safe and effective. The safety requirement is derived from the Federal Food Drug and Cosmetic Act of 1938 (FD&C Act). The effectiveness requirement stems from a 1962 amendment to the Act. Subsequent judicial rulings established that effectiveness means an effect that is clinically meaningful (e.g., improved survival, decreased rate of important events such as stroke, heart attack, beneficial effect on symptoms, etc,)

or there is an effect on an established surrogate endpoint. A surrogate endpoint is a laboratory measure or physical sign used as a substitute for a clinically meaningful endpoint. Treatment-induced changes in a surrogate endpoint are expected to reflect proportional changes in a clinically meaningful endpoint.

In 1992, the NDA and BLA regulations were amended (Subparts H and E, respectively) to allow for "accelerated approval" in diseases that are serious or life-threatening. Under accelerated approval regulations, for indications where the new product appears to provide benefit over available therapy, accelerated approval may be granted on the basis of a surrogate endpoint that is "reasonably likely" to predict clinical benefit. Under accelerated approval, the applicant is required to study the drug further to verify and describe its clinical benefit. Postmarketing studies would usually be underway at the time of accelerated approval. These post-marketing confirmatory studies (also known as post-marketing requirements) may be either a new trial or completion and final follow-up of patients on an existing trial. In either case, the required post-marketing study must show an effect on an endpoint that reflects clinical benefit. If those studies fail to demonstrate clinical benefit, or if the applicant does not show "due diligence" in completing the trial(s), the regulations describe a process for removing the product from the market.

Previously Received Advice from the ODAC
On February 8, 2011, the Office of Oncology Drug Products convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the status of drugs approved under the accelerated approval regulations; the following advice was offered from the committee:

Overall, ODAC members agreed that randomized controlled trials should be the standard and that single arm trials should be the exception. Committee members commented that single arm trials may be used in the following situations: 1) rare diseases and 2) high level of activity of the agent or pronounced treatment effect. It was also mentioned that the toxicity of the agent must be taken into account in a risk/benefit analysis in the situations in which single arm trials may be used. Committee members noted that it would be helpful to have a definition of rare diseases. Members also noted that the bar for accelerated approvals should not be lowered to move products on to the market faster through single arm trials, but rather single arm trials should only be used in certain situations and randomized controlled trials should be the standard.

Overall, members agreed that at least two controlled trials should be needed for accelerated approval commitments. Most members agreed with this statement with the caveat that in rare diseases and pediatrics this may not be feasible.

Overall, members felt that a well designed development plan is needed prior to the application being filed. Most also preferred that the sponsor have studies already ongoing at the time of application.

4. Clinical Studies

4.1. Study VSLI-06 Design and Results

Study VSLI-06, as the supportive study for this proposed indication, was a Phase 1/2, multicenter, open-label, dose escalation study of Marqibo combined with dexamethasone. Patients were required to have relapsed or refractory ALL and to have measurable disease. The Phase 1 portion of the study was designed to define the MTD of Marqibo. A total of 36 patients were enrolled in the study and received at least 1 dose of Marqibo plus dexamethasone, of which 26 patients (72.2%) were included in the MTD evaluable population. Because of DLTs at the 2.4 mg/m^2 dose level (motor neuropathy of Grade 3, grand mal seizure of Grade 4, and elevated AST and hyperbilirubinemia of Grade 4 in three patients) the 2.25 mg/m^2 dose administered weekly was declared the MTD.

Applicant reported an overall response rate (CR+PR) of 22.2% (4 out of 18 patients in the 2.25 mg/m^2 dose cohort, 95% CI: 6.4 - 47.6) and a CR rate of 16.7% (3 out of 18 patients, 95% CI: 3.6-41.4) in this Study. On the basis of these results from the phase 1 portion of the study, applicant decided to open a different Phase 2 clinical trial (Study HBS407) instead of continuing with the Phase 2 portion of this study.

4.2. Study HBS407 Design

Study HBS407 was a Phase 2, international, multicenter, open-label, single-arm trial to evaluate the effect of Marqibo in adult patients with Ph- ALL or lymphoblastic lymphoma in second or greater relapse, or Ph- ALL or lymphoblastic lymphoma who failed 2 or greater treatment lines of anti-leukemia chemotherapy. Eligible patients had to have achieved a CR to at least 1 prior, but not necessarily the immediately prior, anti-leukemia chemotherapy, defined by a leukemia-free interval of ≥ 90 days.

Patients had to be ineligible for immediate HSCT at the time of screening and enrollment. According to the applicant, patients were enrolled into this single-agent Phase 2 study because of anticipated intolerance of multi-agent therapy (e.g., poor marrow reserves or poor performance status), a lack of standard of care in the salvage setting, refractoriness to prior multi-agent therapy, relapse following multi-agent therapy and a relatively short remission duration, or relapse following HSCT and a relatively short remission duration. Concomitant corticosteroids were not permitted beyond Day 5 of Course 1 with the intention to isolate the treatment effect of Marqibo.

Eligible patients received IV Marqibo at 2.25 mg/m^2 (MTD in the phase 1/2 supporting Study VSLI-06), based on actual BSA over 60 minutes. Dosing was administered every 7 days (±3 days) on Days 1, 8, 15, and 22 with no less than 4 days between dosing. Four weekly doses of VSLI constituted 1 course (cycle) of study treatment. Before each scheduled dose of VSLI, the patient was to be evaluated for possible toxicities, particularly neurotoxicity, that may have occurred after the previous doses.

Bone marrow aspirate and biopsy were to be performed on Day 28 of designated study treatment cycles. For those patients with <10% bone marrow blasts and evaluable extramedullary disease, imaging and/or biopsy of the extramedullary disease site should have been obtained in addition to BM aspirate and biopsy. Those patients who did not have disease progression and unacceptable study treatment-related toxicity were eligible for continued VSLI treatment until HSCT, disease progression, or PI determination that VSLI treatment was no longer beneficial. If at any time a response of CR or CRi was documented in a bone marrow examination, a confirmatory bone marrow aspirate and biopsy were to be performed 4 weeks later on Day 28 of the next study treatment course. After confirming CR or CRi, bone marrow aspirate and biopsy were to be performed at the end of every other course of study treatment (Day 28, ± 3 days) for up to 6 months after the initial CR or CRi assessment. At the End-of-Therapy Visit (30 days [+5 days] after the last VSLI dose), or prior to any subsequent anti-leukemia therapy, patients were to undergo bone marrow aspirate and biopsy assessments.

The primary efficacy endpoint of Study HBS407 was the proportion of patients who achieved CR+CRi, as determined by IRRC and PI using IWG Criteria.[8] The key secondary efficacy endpoints included 1) CR+CRi duration defined by the applicant as "time, in days, from first CR or CRi until recorded (or inferred) relapse and was only defined for patients who achieved CR or CRi", 2) time to CR or CRi, 3) OS, 4) leukemia-free survival, and 5) number and proportion of patients who received post-VSLI HSCT. Per FDA Guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", single-arm trials do not adequately characterize time-to-event endpoints such as survival, time-to-progression, or progression free survival.

Two analysis datasets were utilized for the analysis of efficacy: 1) Treated Analysis Set which included all patients who received at least one dose of study drug and had histologically and molecularly proven Ph- ALL that was confirmed by a central hematopathologist, 2) IRRC Evaluable Analysis Set that included patients who had reviewable data for IRRC to assess and determine response or lack of response.

4.3. Study HBS407 Enrollment

Sixty-eight patients were screened and enrolled into Study HBS407. The Treated population included 65 patients (95.6%) who received at least one dose of study treatment. The IRRC evaluable population included 53 patients (81.5%) of the treated population. There were 12 patients who were not included in the IRRC evaluable analysis set. Protocol specified bone marrow examinations and other assessments to document a response or lack of response to Marqibo were absent for these patients. The most common reason for the lack of these evaluations was death due to infection that occurred prior to the first scheduled assessment. Ten out of 12 patients died within 40 days of treatment.

The patients' demographics and disease characteristics are summarized in the following tables.

Table 1. Demographic Characteristics of Patients in Study HBS407 (Treated population)

Variable at baseline	N=65
Gender	n(%)
Female	32 (49.2)
Male	33 (50.8)
Race	n(%)
White	56 (86.2)
Black or African American	4 (6.2)
Asian	2 (3.1)
Other	3 (4.6)
Age group (range 19-83 years old)	n(%)
18-29 years	29 (44.6)
30-59 years	28 (43.1)
≥60 years	8 (12.3)

Source: NDA 202497, Module 5, HBS407 CSR, Tables 14.1.6.1 through 14.1.6.2

Table 2. Baseline Characteristics of Patients in Study HBS407 (Treated population)

Baseline Parameter	N=65
Type of ALL (based on Central Reviewer)	n (%)
Precursor B-lymphoblastic leukemia	55 (84.6)
Precursor T-lymphoblastic leukemia	10 (15.4)
Time Since Diagnosis of ALL	Years
Median	1.8
Min, Max	< 1, 15
Extramedullary Disease	n (%)
Yes	10 (15.4)
No	55 (84.6)
ECOG Performance Status	n (%)
0	17 (26.2)
1	33 (50.8)
2	11 (16.9)
3	4 (6.2)
Platelet Count	
$\leq 50 \times 10^9$/L	39 (60.0)
$> 50 \times 10^9$/L	26 (40.0)

Source: NDA 202497, Module 5, HBS407 CSR, Tables 14.1.6.1 through 14.1.7.2, Tables 14.1.7.5 through 14.1.7.7, and Table 14.1.7.10.)

Table 3. Baseline Cytogenetics of Patients in Study HBS407 (Treated population)

Findings	**N = 65**
Intermediate Cytogenetics n (%)	23 (35.4)
Normal	20 (30.8)
del	2 (3.1)
-Y	1 (1.5)
Unfavorable Cytogenetics n (%)	33 (50.8)
complex karyotypes	19 (29.2)
-7/del(7q)	2 (3.1)
+8	1 (1.5)
-7/del(7q)/+8	1 (1.5)
del (5q)/-5q	1 (1.5)
abnl 11q	2 (3.1)
abnl 21q	2 (3.1)
abnl 17p	1 (1.5)
abnl 9q	2 (3.1)
abnl 21q and abnl 17p	1 (1.5)
abnl 21q and abnl 9q	1 (1.5)
Missing	9 (13.9)

Source: NDA 202497, Module 5, HBS407 CSR, Table 14.1.7.4 and Table 14.1.7.9

Table 4. Study HBS407 - Prior Anti-leukemia Therapy (Treated population)

Therapy Type	**N = 65**
Number of Prior Lines of Anti-Leukemia Treatment (%)	n (%)
2	33 (50.8)
3	24 (36.9)
4	7 (10.8)
6	1 (1.5)
Prior HSCT	n (%)
None	34 (52.3)
One Prior HSCT	29 (44.6)
Two Prior HSCT	2 (3.1)
Best Response to Prior Induction Therapy	n (%)
Complete Remission (CR)	62 (95.4)
Progressive Disease and No Response	2 (3.1)
Unknown	1 (1.5)
Duration of Best Response to Prior Induction Therapy*	Days
Median	334
Min, Max	32, 4050

*The data for duration of best response to prior induction therapy are missing for14 patients. The values for this variable are based on data from 51 patients.
Source: NDA 202497, Module 5, HBS407 CSR, Table 14.1.8.1 and Table 14.1.8.3

Table 5. Study HBS407 - Prior Anti-leukemic Agents (Treated population)

Chemotherapy used	first-line	second-line
vincristine	100%	93.8%
cyclophosphamide	93.8%	81.5%
methotrexate	92.3%	78.5%
cytarabine	89.2%	84.6%
doxorubicin	89.2%	72.3%

Source: NDA 202497, Module 5, HBS407 CSR, Table 14.1.8.2.

Approximately 34% (22 out of 65) of patients did not receive asparaginase or peg-asparaginase prior to enrollment which is an approved and therefore available therapy for the treatment of Ph- ALL.

Seven out of 10 patients with T-cell ALL did not receive nelarabine, an approved agent, as one of their prior anti-leukemic therapy before enrollment.

Study Treatment and Concomitant Corticosteroid Use:

In Study HBS407, Marqibo was administered at a dose of 2.25 mg/m^2 IV every 7 days as a 60 minute infusion for a 28 day course of treatment. Corticosteroid use was prohibited during the study and patients had to be tapered off of systemic steroids by Day 5 of Course 1. Systemic steroids were prescribed beyond Day 5 of Course 1 for 16 patients (16/65, 24.6%), including 4 patients with CR+CRi assessed by PI. Overall, 6 different corticosteroids were used after Day 5 of Course 1 at varying doses including methylprednisolone IV or oral at doses ranging from 12 to 125 mg, hydrocortisone IV at doses ranging from 20 to 100 mg, dexamethasone IV or oral at doses ranging from 1 to 40 mg, oral prednisone at doses ranging from 5 to 40 mg, prednisolone IV at a dose of 50 mg, budesonide inhaled at a dose of 90 mcg. For 4 CR+CRi patients assessed by PI the following corticosteroid use were reported: 1) three IV doses of hydrocortisone 20 mg, 25 mg, and 100 mg on Study Days 3, 31, and 33 as well as daily oral prednisone 20 mg from Study Days 42 to 64, 2) oral prednisone (5-20 mg) taper from Study Days 22 to 43, 3) IV dexamethasone 1 mg daily for 5 days from Study Days 12 to 16, and 4) oral dexamethasone 6 mg daily for 4 days from Study Days 5 to 8.

5. Major Efficacy Findings

CR or CRi Rates:

The Applicant reported, based on PI assessment, the number of CR+CRi was 13 and based on IRRC assessment, the number of CR+CRi was 11 (8 CRs and 3 CRis). The PI assessment included two cases of CR+CRi which were bone marrow blast responses, which represent CR without recovery of both neutrophil and platelet counts, by IRRC assessment. The FDA CR+CRi rates based on case report forms (CRFs) in treated patient population from Study HBS407 are summarized in Table 6.

Table 6. FDA Review of CR+CRi Rates Based on Review of CRFs (Treated population)

	CR+CRi FDA Based on CRFs Review (N=65)	
	Confirmed	Confirmed + Unconfirmed*
CR+CRi [n(%)] Exact 95% CI in %	8 (12.3) (5.5, 22.8)	10 (15.4) (7.6, 26.5)
Complete Remission (CR) [n(%)] Exact 95% CI in %	2 (3.1) (0.4, 10.7)	3 (4.6) (1.0, 12.9)
CRi (including CRp) [n(%)] Exact 95% CI in %	6 (9.2) (3.5, 19.0)	7 (10.8) (4.5, 21.0)

*Unconfirmed - no repeat bone marrow evaluation to confirm the response
Source: NDA 202497 – Case Reports Forms (Module 5)

The FDA response assessment that included all patients who received at least one dose of study drug was not in complete agreement with the applicant's. FDA's assessment found that 10 patients' disease status was a CR or CRi with treatment. FDA review of the CRFs provided in the initial submission suggested that one patient's BM persistently contained >5% blasts, hence could not be considered as CR or CRi. The review team queried the Applicant regarding this one case. The Applicant stated that "Course 1 Day 28 and Course 3 Day 28 case report forms appear to have been misfiled in a manner that could lead one to conclude that there was reviewer discordance where there was actually none". Table 7 summarizes the bone marrow assessments for this patient. Compared to the initial submission, in the amended submission the central pathology reviews were switched between course 1 and course 3. The dates on which bone marrow examinations were performed are not indicated on the central pathology review forms and this case may need additional documentation to determine final status.

Table 7. Summary of Bone Marrow Assessment for the Patient with Pending Final Status

Bone Marrow Assessments by Pathologists	Course 1, Day 28 (June 2008)		Course 2 Day 28 (July 2008)	Course 3, Day 28 (Aug 2008)		Course 4 Day 28 (Sep 2008)
	Initial Submission	Amended Submission		Initial Submission	Amended Submission	
Local Marrow Blast (%)	2	No change	20	3	No change	30
Central Marrow Blast (%)	2	25	11	25	2	22
Adjudicator Marrow Blast (%)	10	No change	-	-	-	19

Local, Central and Adjudicator bone marrow blast percentage was based on the highest blast percentage derived following any microscopic, immunohistochemical, and flow cytometry examination of bone marrow aspirate and biopsy based on the initial submitted and amended Case Reports Forms of this patient (NDA 202497, Module 5).

The final status of this case is pending. However, the best response would be an unconfirmed CRp based on the fact that the platelet count does not rise above

100×10^9/L and the only assessment where the bone marrow blast count is less than 5% is at the end of Cycle 3. The bone marrow assessments at the end of Cycles 1, 2, and 4 showed persistently >5% blasts (i.e. no CR). In addition, the bone marrow report for the end of Cycle 3 could be considered inadequate (no spicules/particles present) for bone marrow sample reported by the central pathology review.

Reviews of local, central and adjudicator pathology reports, CBC results, transfusion history and subsequent anti-leukemic therapies by the FDA, demonstrated that out of 10 CR+CRis, 3 were CRs and 7 were CRis (including CRps). For 8 patients, the initial documented CR+CRi responses were confirmed by at least a subsequent bone marrow aspirate or biopsy and complete blood count (CBC) examinations. Two patients only had one bone marrow biopsy without subsequent biopsies to confirm the initial CR or CRi.

As mentioned in the previous section, 22 (34%) of patients in the treated population did not receive asparaginase products as an available therapy prior to enrollment into Study HBS407. Of the 10 CR+CRi patients, 7 (70%) received asparaginase and 3 (30%) did not receive asparaginase in prior lines of treatment. Of 43 patients who received prior asparaginase, 6 (14%) achieved confirmed CR+CRis. The CR+CRi rates based on prior asparaginase treatment are summarized in Table 8.

Table 8: CR+CRi Rates in Population who Received Available Therapy

Patients	n (%)
Total	43 (100)
Confirmed CR+CRi	6 (14)
Unconfirmed CR+CRi	1 (2.3)

Source: FDA reviewer's analysis

Duration of CR or CRi:

FDA assessment of duration of remission was based on the first date of CR+CRi to the date of the last available assessment of the same response. The Applicant's, duration of response used time, in days, from first CR or CRi until recorded (or inferred) relapse which included the period after transplant or other subsequent chemotherapies.

By FDA assessment, five out of 8 confirmed CR+CRi patients had duration of response less than one month. The median duration of response for these 8 confirmed CR+CRis was 28 days. Table 9 demonstrates the duration of CR/CRp/CRi by both IRRC and FDA assessments.

Table 9. CR+CRi and Duration of CR+CRi by IRRC and FDA

Subject	IRRC Assessment		FDA Assessment Based on CRFs		
	Response	CR/CRi Duration (days)	Response	CR/CRi Duration (days)	FDA Comments
Patients who received Prior Asparaginase Products					
1	CRi	42	CRi	7	BMBx#2 was obtained 7 days after BMBx#1 Received new therapy 16 days after BMBx#2
2	CR	35	CR	Unable to assess	BMBx#1 - "inadequate and non-diagnostic" BMBx#2 - CR No further BM assessment Off study due to AE/disease progression less than 1.5 months after BMBx#2
3	CR	463	CRi	36	BMBx#1 - CR BMBx#2 - CRi Conditioning chemotherapy for allo-HSCT 3 days after BMBx#2
4	CR	162	CR	28	BMBx#1 - CR BMBx#2 - CR Patient discontinued study due to AEs, and received subsequent chemotherapies 33 days after BMBx#2
5	CR	162	CRi	63**	BMBx#1 - CRi BMBx#2 - CRi BMBx#3 - CRi BMBx#4 - CR Conditioning chemotherapy for allo-HSCT 2 days after BMBx#4
6	CR	144	CRi	151**	BMBx#1 - CRi BMBx#2 - CRi BMBx#3 - CR BMBx#4 - CRi BMBx#5 - CRi BMBx#6 - CR Patient withdrew consent and went to hospice after the last BMBx.
7*	CR	166	CR	28	Kidney Biopsy#1 - CR Kidney Biopsy#2 - CR Patient discontinued study due to AEs 20 days after kidney Biopsy#2
8	CR	32	Pending**	Unable to assess	see Table 7
Patients who did not receive Prior Asparaginase Products					
9	CRi	132	CRi	Unable to assess	BMBx#1 - CRi Conditioning chemotherapy for allo-HSCT 9 days after BMBx#1
10	CR	135	CRi	26	BMBx#1 - CRi BMBx#2 - CR Conditioning chemotherapy for allo-HSCT 24 days after BMBx#2
11	CRi	210	CRi	28	BMBx#1 - CRi (with radiographic resolution of extramedullary disease) BMBx#2 - CRi allo-HSCT 34 days after BMBx#2

*Extramedullary ALL in kidney, negative bone marrow examination.
**These cases are under review based on further information from applicant.
Source: NDA 202497 Module 5, CRFs and Listing 16.2.3.5.1 and Listing 16.2.3.5.2 and FDA reviewer's analysis.

Subsequent Stem Cell Transplantation:
Twelve patients in Study HBS407 received stem cell transplantations after receiving Marqibo. Of these 12 patients, 5 achieved CR or CRi or CRp with Marqibo treatment and underwent HSCT. Seven patients did not achieve CR or CRi. Six of these 7 patients who did not achieve CR/CRp/CRi received multi-agent chemotherapy regimens pre-transplant and underwent subsequent HSCT. Further information on subsequent treatment for one patient who underwent HSCT was not available. These data indicate that patients whose disease did not achieve a CR, CRi or CRp were candidates for other therapy. Patients underwent HSCT regardless of achieving CR or CRi after Marqibo administration.

Long-term survivors:
Five patients who lived for more than 1 year after enrollment in Study HB407 were considered "potential long-term survivors as a result of VSLI". By IRRC response assessments, two of the five patients did not respond to Marqibo. Reviews of CRFs showed that one patient had >25% blasts in bone marrow after 4 doses of Marqibo and discontinued Marqibo after 3 more doses because of severe neuropathy. The patient refused to have subsequent bone marrow biopsy examinations. This patient was followed by his local oncologist and received methotrexate, L-asparaginase and transfusion support and lived approximately 19 months after the last dose of Marqibo.

The second patient was enrolled in Study HBS407 following the third ALL relapse and received 2 doses of VSLI as fourth salvage treatment. The patient discontinued the study due to hyponatremia secondary to syndrome of inappropriate antidiuretic hormone (SIADH) and continued to have residual peripheral neuropathy in the subsequent 12 months of follow up. Bone marrow biopsy at the end of the study visit was read by both local and central pathologists as showing approximately 90% blasts. According to CRF, this patient received subsequent corticosteroids and chemotherapy and died approximately 21 months after the last dose of Marqibo.

The third patient received only a single dose of Marqibo with dexamethasone and was withdrawn from the study due to receipt of concomitant dexamethasone. The patient underwent a second allogeneic HSCT. The fourth patient had a history of autologous transplantation after the first relapse. Bone marrow at staging showed 0% blasts and biopsy of para-spinal mass resulted in the diagnosis of precursor T-cell leukemia. This patient had persistent extramedullary disease after enrollment, discontinued study treatment due to Grade 3 neuropathy, and subsequently received more anti-leukemia therapies as well as allogeneic HSCT. The fifth patient was enrolled in Study HBS407 and received 7 doses of VSLI totaling 25.2 mg as third salvage therapy. She achieved a confirmed CRi and subsequent CR that was followed by a planned HSCT with resultant long-term survival.

Patient Disposition:
Treatment was ultimately discontinued in all 65 patients (100%) in the treated population of Study HBS407. The most common reason for study treatment discontinuation was disease progression (40.0%, 26/65), followed by adverse events (36.9%, 24/65), investigator request (9.2%, 6/65), planned HSCT (7.7%, 5/65), and patient withdrew consent (6.2%, 4/65).

6. Major Safety Findings

The review of Marqibo safety profile for NDA 202497 includes the safety data from the 101 patients in Phase 1/2 Study VSLI-06 and Phase 2 Study HBS407, with particular focus on the 83 (65 in HBS407 and 18 in VSLI-06) patients who were treated with weekly VSLI at a dose of 2.25 mg/m^2.

Overall Exposure: Of the 83 patients initially treated with VSLI at a dose of 2.25 mg/m^2, 61 (73.5%), 25 (30.1%), 4 (4.8%), and 3 (3.6%) completed treatment cycles 1, 2, 3, and 4, respectively, Table 10.

Table 10. Patients on Treatment by Course

Courses Completed	2.25 mg/m^2, N = 83 (%)	Total, N = 101 (%)
1	61 (73.5)	74 (73.3)
2	25 (30.1)	32 (31.7)
3	4 (4.8)	4 (4)
4	3 (3.6)	3 (3)

Source: NDA 202497, Integrated Summary of Safety Tables, Table 1.3

Summary of Adverse Events: As displayed in Table 11, all patients in studies HBS407 and VSLI-06 reported AEs. Overall, 80 out of 83 (96.4%) patients who received 2.25 mg/m^2 Marqibo reported AEs of Grade ≥3 and 75.9% (63/83) of patients reported serious AEs.

Table 11. Overall Summary of Adverse Events

Adverse Event Category	2.25 mg/m^2		
	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)
Any Adverse Event	18 (100.0)	65 (100)	83 (100)
Any Grade ≥ 3 Adverse Event	18 (100.0)	62 (95.4)	80 (96.4)
Any Adverse Event with Outcome of Death	3 (16.7)	21 (32.3)	24 (28.9)
Any Serious Adverse Event	17 (94.4)	46 (70.8)	63 (75.9)
Any Adverse Event Leading to Discontinuation	1 (5.6)	22 (33.8)	23 (27.7)

Source: NDA 202497, Integrated Summary of Safety Tables, Table 3.2.2

AEs experienced by ≥10% of patients (overall) included constipation (57.4%), nausea (51.5%), pyrexia (42.6%), fatigue (40.6%), peripheral neuropathy (38.6%), febrile neutropenia (37.6%), diarrhea (36.6%), anemia (33.7%), decreased appetite (32.7%), and insomnia (31.7%).

Adverse Events Grade ≥3: Table 12 summarizes any adverse events Grade ≥3 in ≥5% of patients who received 2.25 mg/m^2 Marqibo in Studies HBS407 or VSLI-06 by System Organ Class. Neuropathy-related AEs are reported in Table 14 in further detail.

Table 12. Adverse Events Grade ≥3 in ≥5% of Patients Received 2.25 mg/m^2 Marqibo in Studies HBS407 or VSLI-06

Adverse Events Grade ≥3	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)
Blood and Lymphatic System Disorders	12 (66.7)	35 (53.8)	47 (56.6)
Febrile Neutropenia	5 (27.8)	21 (32.3)	26 (31.3)
Neutropenia	4 (22.2)	11 (16.9)	15 (18.1)
Anemia	6 (33.3)	8 (12.3)	14 (16.9)
Thrombocytopenia	3 (16.7)	11 (16.9)	14 (16.9)
Infections	10 (55.6)	23 (35.4)	33 (39.8)
Pneumonia	0	7 (10.8)	7 (8.4)
Septic Shock	1 (5.6)	4 (6.2)	5 (6.0)
Staphylococcal Bacteremia	4 (22.2)	1 (1.5)	5 (6.0)
Neuropathy-Related AEs	3 (16.7)	24 (36.9)	27 (32.5)
Peripheral Sensory and Motor Neuropathy	1 (5.6)	13 (20.0)	14 (16.7%)
Constipation	2 (11.1)	2 (3.1)	4 (4.8)
Ileus, Colonic Pseudo-Obstruction, Subileus	0	5 (7.7)	5 (6.0)
Asthenia	0	4 (6.2)	4 (4.8)
Muscular Weakness	1 (5.6)	0	1 (1.2)
Respiratory Thoracic and Mediastinal Disorders	5 (27.8)	12 (18.5)	17 (20.5)
Respiratory Distress	2 (11.1)	3 (4.6)	5 (6.0)
Respiratory Failure	1 (5.6)	3 (4.6)	4 (4.8)
General Disorders and Administration Site Condition	8 (44.4)	23 (35.4)	31 (37.3)
Pyrexia	5 (27.8)	7 (10.8)	12 (14.5)
Fatigue	3 (16.7)	7 (10.8)	10 (12.0)
Pain	1 (5.6)	6 (9.2)	7 (8.4)
Gastrointestinal Disorders	8 (44.4)	13 (20.0)	21 (25.3)
Abdominal Pain	4 (22.2)	3 (4.6)	7 (8.4)
Investigations	6 (33.3)	14 (21.5)	20 (24.1)
Aspartate Aminotransferase Increased	2 (11.1)	4 (6.2)	6 (7.2)
Vascular Disorders	3 (16.7)	5 (7.7)	8 (9.6)
Hypotension	3 (16.7)	2 (3.1)	5 (6.0)
Psychiatric Disorders	4 (22.2)	5 (7.7)	9 (10.8)
Mental Status Changes	1 (5.6)	2 (3.1)	3 (3.6)
Cardiac Disorders	3 (16.7)	6 (9.2)	9 (10.8)
Cardiac Arrest	2 (11.1)	3 (4.6)	5 (6.0)
Renal and Urinary Disorders	1 (5.6)	5 (7.7)	6 (7.2)
Musculoskeletal and Connective Tissue Disorders	1 (5.6)	6 (9.2)	7 (8.4)

Source: NDA 202497, Integrated Summary of Safety Tables, Table 3.2.6

The most common treatment-related AEs included constipation (40.6%), peripheral neuropathy (36.6%), nausea (22.8%), hypoesthesia (19.8%), paraesthesia (18.8%), neutropenia (17.8%), fatigue (16.8%), anemia (12.9%), thrombocytopenia (10.9%), and abdominal pain (11.9%). The incidences of these events were similar across dose groups.

AEs Leading to Dose Discontinuation or Dose Modification: The most frequently reported AEs leading to study drug discontinuation in 83 patients who received 2.25 mg/m^2 Marqibo in Studies HBS407 and VSLI-06 were peripheral neuropathy in 8 (9.6%), leukemia-related in 6 (7.2%), and tumor lysis syndrome in 2 (2.4%). AEs potentially related to neuropathy and reported each in one patient included decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain.

Approximately one-half of the 83 patients (53%) who began treatment with 2.25 mg/m^2 VSLI actually received the intended prescribed dose and dosing schedule. Of the remaining patients, 17 (20.5%) missed doses, 18 (21.7%) had reduced doses, and 5 (6.0%) had delayed doses. The majority of missed doses occurred in the presence of a new AE. More than one third of patients (6 of 17 patients, 35%) missed doses due to AEs associated with neuropathy including peripheral neuropathy, pain in extremities, facial neuralgia, and ileus. Neuropathies are the most notable adverse events associated with vincristine. The number of patients who required neuropathy-related dose reduction, dose delay and missed doses do not suggest a better toxicity profile for Marqibo than vincristine.

Serious Adverse Events: A total of 63 of 83 patients (75.9%) who received 2.25 mg/m^2 VSLI reported at least one AE that was classified as serious (SAEs). In this population, the most frequently reported SAEs included febrile neutropenia (17, 20.5%), pyrexia (11, 13.3%), respiratory distress and respiratory failure (9, 10.8%), hypotension (6, 7.2%), pneumonia (5, 6%), cardiac arrest (5, 6%) and peripheral neuropathy (5, 6%) (Source: ISS Tables, Tables 3.2.14 and 3.2.15).

Deaths: All patients in Study HBS407 were to be followed for survival, while no long-term follow-up was conducted for Study VSLI-06, hence the number of deaths in Study VSLI-06 is underreported. Sixty out of 65 patients in study HBS407 died during the follow up period. In study HBS407, 15 (23.1%) patients died during the treatment period (i.e. deaths that occurred after the first dose infusion date through last dose date plus 30 days), Table 13.

Table 13. Overall Summary of Deaths

Time of Death	**2.25 mg/m^2**	
	VSLI-06, (N=18) n (%)	**HBS407, (N=65) n (%)**
Deaths During Treatment Period	4 (22.2)	15 (23.1)
Deaths During Follow-up	2 (11.1)	45 (69.2)

Source: NDA 202497, Integrated Summary of Safety, Tables 3.2.21.1 and 3.2.21.2

The most common reported causes of death in Study HBS407 were ALL (42, 64.6%) and complications of HSCT (3, 4.6%). The remaining 15 deaths were reported to be caused by a brain infarct (1), intracerebral hemorrhage due to CNS leukemia (1), large cerebellar hemorrhage (1), liver failure (1), multi system organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1).

Neuropathy: A total of 72 (86.7%) of the 83 patients on 2.25 mg/m^2 VSLI reported a neuropathy-associated AE during the treatment period. The most common neuropathy-associated AEs for this patient population were constipation (56.6%), peripheral neuropathy (37.3%), paresthesia (22.9%), hypoesthesia (22.9%), asthenia (19.3%), arthralgia (18.1%), and myalgia (14.5%). Table 14 presents neuropathy-related AEs of Grade ≥3 severity and any neuropathy-related SAEs for patients being treated with Marqibo 2.25 mg/m^2. Each patient might have reported more than one AE.

Table 14. Neuropathy-related Adverse Events of Grade ≥3 Severity and Any Neuropathy-related Serious AEs for Patients Who Received Marqibo 2.25 mg/m^2 in Studies HBS407 and VSL-06

Neuropathy-Related Adverse Events	VSLI-06 (N=18), n (%)	HBS407 (N=65), n (%)	Total (N=83), n (%)
Any Grade ≥3 Neuropathy-Related AEs	3 (16.7)	24 (36.9)	27 (32.5)
Peripheral Sensory and Motor Neuropathy	1 (5.6)	13 (20.0)	14 (16.7%)
Paraesthesia and Hypoaesthesia	0	2 (3.1)	2 (2.4)
Decreased Vibratory Sense	0	1 (1.5)	1 (1.2)
Constipation	2 (11.1)	2 (3.1)	4 (4.8)
Ileus, Colonic Pseudo-Obstruction, Subileus	0	5 (7.7)	5 (6.0)
Asthenia	0	4 (6.2)	4 (4.8)
Gait Disturbance	0	1 (1.5)	1 (1.2)
Pain In Extremity	0	2 (3.1)	2 (2.4)
Areflexia	0	1 (1.5)	1 (1.2)
Arthralgia	0	1 (1.5)	1 (1.2)
Muscular Weakness	1 (5.6)	0	1 (1.2)
Any Neuropathy-Related SAEs	1 (5.6)	10 (15.4)	11 (13.3)
Peripheral Sensory and Motor Neuropathy	0	6 (9.2)	6 (7.2)
Constipation	1 (5.6)	2 (3.1)	3 (3.6)
Ileus and Subileus	0	2 (3.1)	2 (2.4)
Gait Disturbance	0	1 (1.5)	1 (1.2)
Facial Palsy	0	1 (1.5)	1 (1.2)

Source: NDA 202497, Integrated Summary of Safety, Table 3.2.20.1.8 and Table 3.2.20.1.9

7. Confirmatory Study

The proposed confirmatory study (TTX404) is a phase 3, multicenter, randomized study to evaluate the substitution of Marqibo for standard vincristine sulfate injection in the induction, intensification, and maintenance phases of combination chemotherapy in the treatment of patients ≥ 60 years old with newly diagnosed acute lymphoblastic leukemia (ALL). The primary endpoint of the study is OS with HR = 0.70. The proposed sample size is 348. As of February 22, 2012, 3 US sites are active and open to enrollment and 14 US sites have completed feasibility and are pending activation. No subjects have been enrolled into this study as of February 22, 2012.

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